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| 09/692,623 | 10/20/2000 | Stephen M. Boyle | 031786-046 | 2200 |

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| EXAMINER |
|---|
| GRASER, JENNIFER E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/692,623 | Boyle et al. |
| **Examiner** | **Art Unit** |
| Jennifer Graser | 1645 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Prel. Amendt. A* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *24-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *24-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

## DETAILED ACTION

Claims 24-34 are currently pending and under examination.

### *Specification*

1. The first line of the specification should be amended to include the current status of parent application 09/091,521, i.e., now U.S. Patent No. 6,149,920.

### *Claim Rejections - 35 USC § 112*

2. Claims 24-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites "a vertebrate at risk or suffering from a pathogenic micro-organism". The phrase should be amended to recite "a vertebrate at risk or suffering from a disease caused by a pathogenic micro-organism".

### *Claim Rejections - 35 USC § 102*

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

4. Claims 24 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Highlander et al. (US 6,180,112).

Highlander et al. discloses whole cell vaccine compositions comprising a recombinant, avirulent *Pasteurella haemolytica* organism which comprises a strong leukotoxin promoter which allows for homologous overexpression of said leukotoxin antigen. The *P.haemolytica* transcriptional activator is introduced on a multicopy plasmid (see bottom of column 42 and claim 8). It is specifically taught that since *P.haemolytica* leukotoxin genes are poorly expressed in *E.coli*, Pasteurella-specific transcriptional factors were used for this homologous, overexpression. Both methods and vaccine for the immunization, prophylaxis or treatment of vertebrates suffering from disease caused by *P.haemolytica* are specifically taught. The use of additional heterologous antigens are also taught. Highlander et al teach homologous over-expression of a desired antigen in an avirulent strain of Gram-negative bacteria and the use of this strain as a vaccine.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 24-26, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kontinen et al (WO 94/19471) in view of Highlander et al. (US 6,180,112).

Kontinen et al disclose a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as increasing gene expression by using multicopy plasmids or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters, resulting in dramatic increases in the synthesis of exoproteins. See page 4, lines 15-20. It is also taught that this method and system may be used with any gram-positive bacterium (page 8, lines 7-8). It also may be used with any desired exoprotein, including any Gram-positive bacterium, antigenic proteins of microbes and protozoa and capsule, outer membrane and fimbria proteins from any Gram-negative bacteria, including *M.tuberculosis, Vibrio cholerae.* It is also taught that any protein toxins or secreted proteins from bacteria, surface proteins of any microorganisms and antigen proteins or viruses may be overexpressed in the same manner as taught in the reference. It is taught that these proteins may be used as vaccines and pharmaceuticals. See page 8, line 11-page 10, line 15. The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The recited host cells used to overexpress the proteins of interest are structurally the same and therefore read on the instant vaccine claims. Additionally, the use of recombinant host cells

which express an antigen that protects against disease, or the isolated antigen itself, were both widely used as vaccines in the prior art at the time the invention was made.

However, Kontinen et al. do not specifically disclose using the over-producing bacterial strains as vaccines, but rather teaches using the over-expressed products from the bacterial strains as the vaccines. Additionally, Kontinen et al. does not specifically recite the use of an attenuated or avirulent strain.

Highlander et al. discloses whole cell vaccine compositions comprising a recombinant, avirulent *Pasteurella haemolytica* organism which comprises a strong leukotoxin promoter which allows for homologous overexpression of said leukotoxin antigen. The *P.haemolytica* transcriptional activator is introduced on a multicopy plasmid (see bottom of column 42 and claim 8). It is specifically taught that since *P.haemolytica* leukotoxin genes are poorly expressed in *E.coli*, Pasteurella-specific transcriptional factors were used for this homologous, overexpression. Both methods and vaccine for the immunization, prophylaxis or treatment of vertebrates suffering from disease caused by *P.haemolytica* are specifically taught. The use of additional heterologous antigens are also taught. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine.

The prior art teaches that the use of multicopy plasmids and/or using strong promoters or multiple promoters was well known in the bacterial art for increasing the production of a desirable protein product. The prior art also teaches that recombinant whole cell vaccines were

well known. Kontinen et al teach that homologous over-expression was well known in the art. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made that not only Gram-positive bacterium, but also attenuated or avirulent Gram-negative bacterium, as evidenced by Highlander et al., could be used to produce an homologous and/or homologous-heterologous expression system for the purpose of producing a vaccine. Highlander et al teaches that the expression system, itself, and not just the isolated expression products make effective vaccines. Further, official notice is taken that it was well known in the prior art that either the recombinant whole cell vaccine or the isolated product of a recombinant whole cell could be used as the major component in a vaccine composition.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 31-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 31-34 are drawn to a method for immunization, *prophylaxis*, or treatment of a vertebrate at risk or suffering from a pathogenic micro-organism, through the administration of a vaccine which comprises an attenuated or avirulent strain of an otherwise pathogenic bacteria of the genus *Mycobacterium* of the genus *Vibrio* and wherein said strain over-expresses at least one homologous antigen encoded by at least one gene from said bacterium and wherein said at least one antigen is capable of inducing a *protective* or therapeutic immune response in the vertebrate against the pathogen.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The prior art teaches that there is no known effective vaccine for the prevention or prophylaxis of *M.tuberculosis*. The prior art also teaches that vaccines against *Mycobacterium* are highly unpredictable. The specification fails to teach a specific antigen whose over-expression would result in protection or treatment in a vertebrate at risk or suffering from a disease caused by *Mycobacterium*. While support may be provided for "treatment", the standard required for "methods of prophylaxis" is much higher. There is no direction or guidance for the

over-expression of a particular gene which would result in protection or prophylaxis of a disease caused by *Mycobacterium*. The prior art fails to teach a working vaccine which will provide protection or prophylaxis against tuberculosis. Further, the specification fails to provide any working examples, such as challenge experiments, which demonstrate the efficacy of the claimed vaccines and methods of prevention. The specification provides written description of over-expressing the groEL gene of *M.tuberculosis* in a *Mycobacterium* species, yet no results of immunization studies, particularly challenge experiments are provided. The examples provided for *Mycobacterium* are merely prophetic. The results provided for Brucella do not correlate to Mycobacterium. These bacterium are very different and antigens which are effective in controlling Brucella do not directly correlate to treating or preventing disease caused by Mycobacterium. Applicant should provide further evidences, specifically challenge experiments, in order to enable the scope of the claims.

Additionally, the specification fails to provide any working examples, such as challenge experiments, which demonstrate the efficacy of the claimed methods of prevention against *Vibrio*. The specification provides written description of over-expressing the ctxB gene of *Vibrio* species, yet no results of immunization studies, particularly challenge experiments are provided. The examples provided for *Vibrio* are merely prophetic. The results provided for Brucella do not correlate to Vibrio. Applicant should provide further evidences, specifically challenge experiments, in order to enable the scope of the claims. Alternatively, Applicant may provide specific teachings in the prior art that the expression product of ctxB was known to provide

immune protection against Vibrio, i.e., challenge experiments are required, (for methods of prophylaxis) or can provide some degree of treatment, i.e., not necessarily challenge experiments, (for methods of treatment).

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

***Note regarding Double patenting***

9. The instant claims were restricted from the claims allowed in US Patent No. 6,149,920 during the prosecution of said parent application, formerly 09/091,521. The instant claims were also restricted from the claims pending in Divisional application 09/692,622 during the prosecution of parent application 09/091,521. Accordingly, a double patenting rejection cannot be made between the instant application and either of the related applications.

10. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J Graser 2/26/02

JENNIFER E. GRASER
PRIMARY EXAMINER